Evolution of Structured BRO Since Last BBS

Frameworks, Quantitative Tools & Regulations

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These are my views not necessarily those of companies, academics or regulators that I am or have been affiliated or worked with.

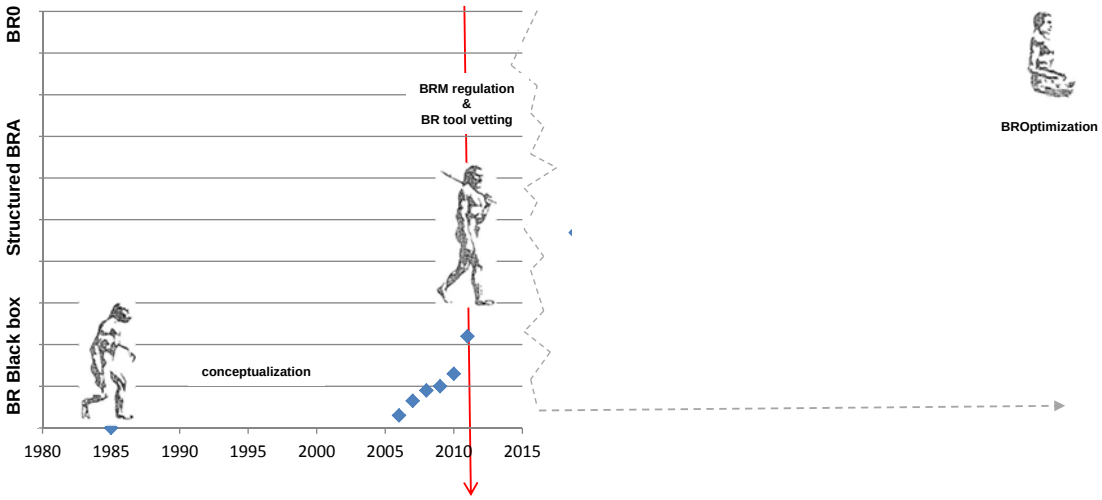
Topics

- evolution of *structured* benefit-risk optimization since last BBS
- update on changing regulatory impact
- current views on relative roles of frameworks and quantitative models

Key Point

Structured BR is here to stay!

.. but like signaling, refinement will take time

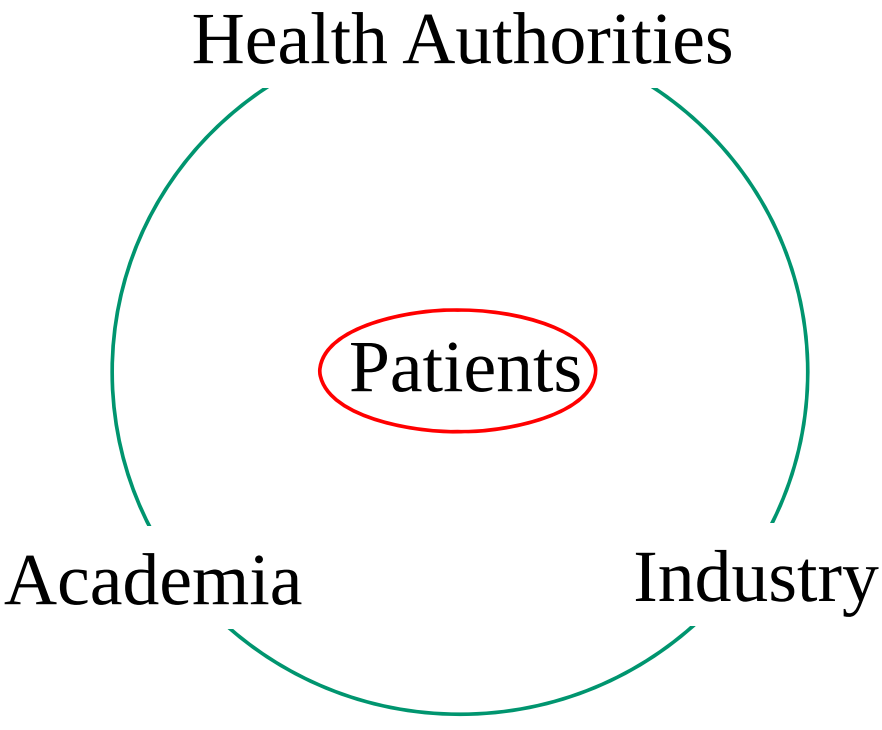


April 2011

“The longest journey begins with a single step” *

*** Tao Tsu**

Stakeholder Perspectives



Industry View

Company Perspectives *

- BR different things to different people
- use BR to inform internal discussions
- case-by-case discussions with HAs
- few use explicit BR framework during approval discussions
- BR requirements *rapidly* increasing (E2c)

*** 2011 PhRMA-Boston Collaborative Group Survey**

A ‘sign of the times’ ...

Pfizer's New Celebrex TV Ads Urge Viewers Balance Risk, Benefit

The advertisements, approved by U.S. regulators, note ... warnings. The commercial then suggests viewers weigh the risks against Celebrex's ability to alleviate arthritis pain ...

“This is going to take those risks head on.”

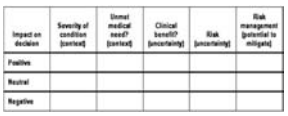
... They open with a women's voice advising viewers that Celebrex, like other NSAIDS, may increase the risks of heart attack, stroke, and bleeding and ulcers in the stomach.

... then lists the drug's benefits ...

By admitting to their risks upfront, drug makers “dial up credibility among consumers” ...

Health Authority Views

Recognizing need for systematic B-R assessments, regulators are developing B-R frameworks

Framework	Characteristics	Background	Status and next steps
FDA 	• Qualitative 'grid' identifying key issues for B-R deliberations • Intended to be used for retrospective explanation of decisions	• Developed with the goal of improving transparency in decision making • Unclear if FDA intent is to apply during approval process or use post-hoc as communication tool only	• Internally piloting framework • Next steps unknown • No roadmap released to date
EMA 	• "Four-fold qualitative model" to improve review quality • Evaluates: – Favorable and unfavorable events – Uncertainty of favorable and unfavorable effects	• Introduced in 2008 • EMA Road Map to 2015 positions B-R as part of EMA's efforts to improve the quality of scientific reviews, proposes shift from risk management plans to "benefit/risk management plans"	• CHMP Assessment Templates have included a list of B-R criteria since Oct. 2009 • B/R Methodology Project (target completion 2011) aims to adapt or develop tools for B-R assessment
CASS[1] 	• Qualitative framework to support regulatory decision making in CASS countries	• Commissioned in 2008 • Led by Centre for Medicines Research (Stuart Walker)	• Currently being piloted

1. CASS denotes the Canada, Australia, Switzerland, and Singapore initiative to develop a B-R framework

FDA Update

- PDUFA re-authorization:
  - includes: a "*patient-focused approach*" to *benefit-risk assessment* in drug development
- CDER is piloting a new benefit-risk framework
  - will become basis of NDA's medical review executive summary
  - intuitive-type of benefit-risk framework
  - person on the street or a MD could look at & understand
  - doesn't have a lot of equations or math in it

FDA Benefit-Risk Framework

- under development
- capture rationale of FDA evaluation of evidence and decision making
- clarify potential reasons for disagreement
- goal is to be intuitive and accessible, while being consistent with detailed analyses

From Baruch Fischhoff, 4/11 FDA/DIA Statistics Forum

FDA Framework

Decision Factor	Evidence and Uncertainties	Conclusions and Reasons
Analysis of Condition	Summary of evidence:	Conclusions (implications for decision):
Unmet Medical Need		
Clinical Benefit		
Risk		
Risk Management		

- **Analysis of Condition**
  - Life-threatening
  - Serious / Non-serious
- **Unmet Medical Need**
  - No approved therapy
  - Limited approved options
  - Sufficient options
- **Clinical Benefit**
  - Outcome of intervention
  - Strength of effect
  - Type of comparative evidence
- **Risk**
  - How well is the safety profile characterized?
  - For each risk:
    - Frequency
    - Severity
    - Rapidity of onset
    - Reversibility
    - Predictability of at-risk population
- **Risk Management**
  - How well will proposed interventions mitigate or inform on risk?

adapted from Bennett Levitan ICSA 2011

Impact on REMS*

* Risk Evaluation and Mitigation Strategies

What is the value of unopposed risk communication?

REMS 'Requirements'

- ensuring " ... that the benefits of the drug outweigh the risks of the drug" is the basis for REMS
- REMS legislation requires that FDA make a benefit-risk assessment
- corollary: REMS cannot be effectively implemented or administered without sufficient assessment of BR

Benefit-Risk in REMS

In evaluating whether to require or modify a REMS FDA must consider:

- the nature of the disease or condition that is to be treated with the drug
- **the expected benefit of the drug** with respect to such disease or condition

July 2010 REMS Public Meeting (FDA)

Next Steps

- FDA developing framework for improving REMS
- launched major initiative to improve patient info
- expects to eventually replace Med Guides with much improved *single* patient information document

FDA's Strategic Plan for Risk Communication

- identifies three areas
  - FDA's science base
  - operational capacity
  - policies and procedures
- requires *action* to improve the agency's ability to *effectively communicate* the *benefits* and *risks* of products under its regulatory control

July 2010 REMS Public Meeting (FDA)

Next Steps

- engaging public through variety of efforts to discuss components of framework
- objective: standardized REMS plugged into existing healthcare systems to address specific risks
- consult prescribers, pharmacists, patient groups, others to get input on designing REMS to preserve access while effectively addressing risk

EMA Update

- IMI Protect
  - Develop methods to strengthen BR monitoring
  - enhance early detection/assessment ADRs from diverse sources
  - enable the integration/presentation of BR data
- EMA Benefit-Risk Assessment Project
  - development/testing
  - tools/processes for balancing multiple benefits and risks to inform regulatory decisions
- ICH E2C
  - proposal to make PSUR the primary tool for implementing regulatory requirement for structured benefit risk

CHMP Assessment Report Template
Benefit-Risk Section

- Section Guidance to Rapporteur on Report
  - "The benefit risk assessment represents the most crucial part of assessment report. ..."
  - "… provide an accurate snapshot of the key benefits and harms, of the strength of evidence and limitations of the data …, and about the benefit risk assessment in the light of the available evidence and therapeutic indication."

adapted from Bennett Levitan ICSA 2011

Impact of BR on PSURS

E2C(R2)

E2c Proposal

- PSUR to be the vehicle for establishing, on an ongoing basis, that the BR balance marketed products remains positive
- PSUR become the primary tool for maintaining authorization and re-authorization
- E2C(R2) will ensure that PSURs will have the role of being periodic benefit-risk evaluation reports for all indications
- PSUR BR evaluation Module with table of contents has been proposed

Health Canada

- 'Technical Discussions on Regulatory Modernization’
- series of 3 multi-day public meetings
- validate proposed activities for regulation throughout product life-cycle
- structured benefit-risk a central theme with emphasis on role in re-authorization

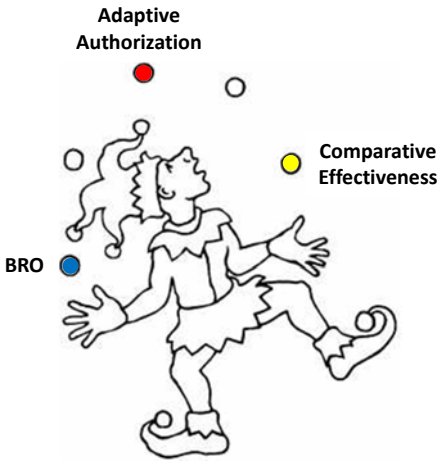
AFSSAPS Update

- AFSSAPS Reform Initiative
- improve assessment of patient benefits
- emphasis on a drug’s “added therapeutic value” over existing therapies as a factor in approval

State-of-the-Art

Academia's View

MIT-CBI NEWDIGS



State-of-the-Art

Patient's View

Key Point

Patients/prescribers want more balanced communication of benefits and risks

A Patient/Prescriber Perspective

"To focus solely on drug safety without consideration of drug benefit, including the severity of the underlying disease or condition, effectiveness of the product under evaluation, and availability and utility of alternative therapies, will create a chilling effect on the development of new treatments for patients most in need of innovation …"

Report distributed by Friends of Cancer Research (FOCR) endorsed by 27 patient and medical groups, including the American Cancer Society and the American Society of Clinical Oncology

Value of Framing

"A problem well put is half solved" *

* John Dewey

Value of Framing

‘ ... can’t build a valid quantitative model without properly framing the problem first’ *

* paraphrasing Larry Phillips

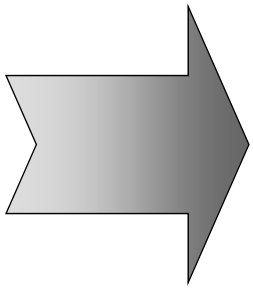
Key Point

Blueprint for making &
Rosetta Stone for deciphering
BR decisions.

… shared understanding through structured dialogue

Value of a BR Framework

- structure
- standardization
- simplification



- transparency
- predictability
- feasibility

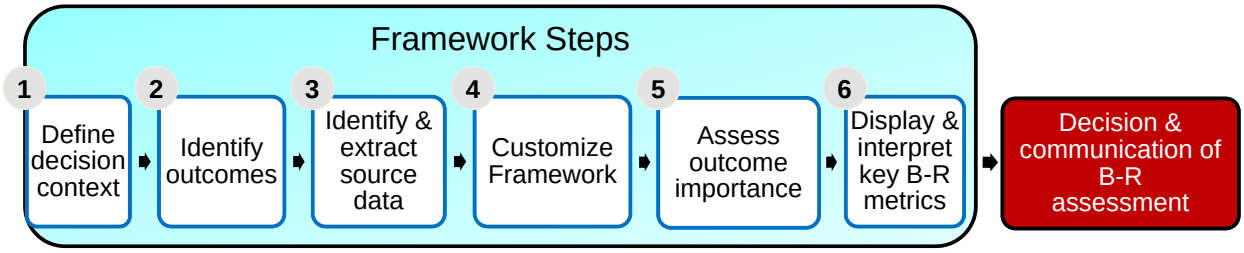
BRAT Framework[1,2]

1. Coplan PM, Noel RA, Levitan BS, Ferguson J, Mussen F. Development of a framework for enhancing the transparency, reproducibility and communication of the benefit-risk balance of medicines. Clinical Pharmacology & Therapeutics 2011; 89: 312-315
2. Levitan BS, Andrews EB, Gilsenan A, Ferguson J, Noel RA, Coplan PM, Mussen F. Application of the BRAT framework to case studies: observations and insights. Clinical Pharmacology & Therapeutics 2011; 89: 217-224

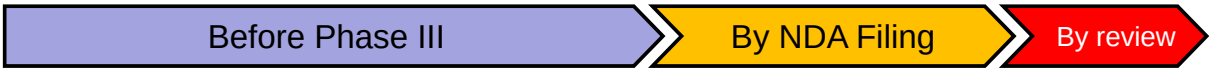
Value Proposition

- organize all relevant inputs to the decision
- simplify data synthesis
- justify data reduction
- characterize gaps in knowledge & uncertainty
- explicitly characterize & record BR decisions
- revisit/review and learn
- build consensus and foster shared understanding across multiple stakeholders

Six steps in the BRAT Framework



Example application: Late development



Framework can be applied at any stage during development or post-approval

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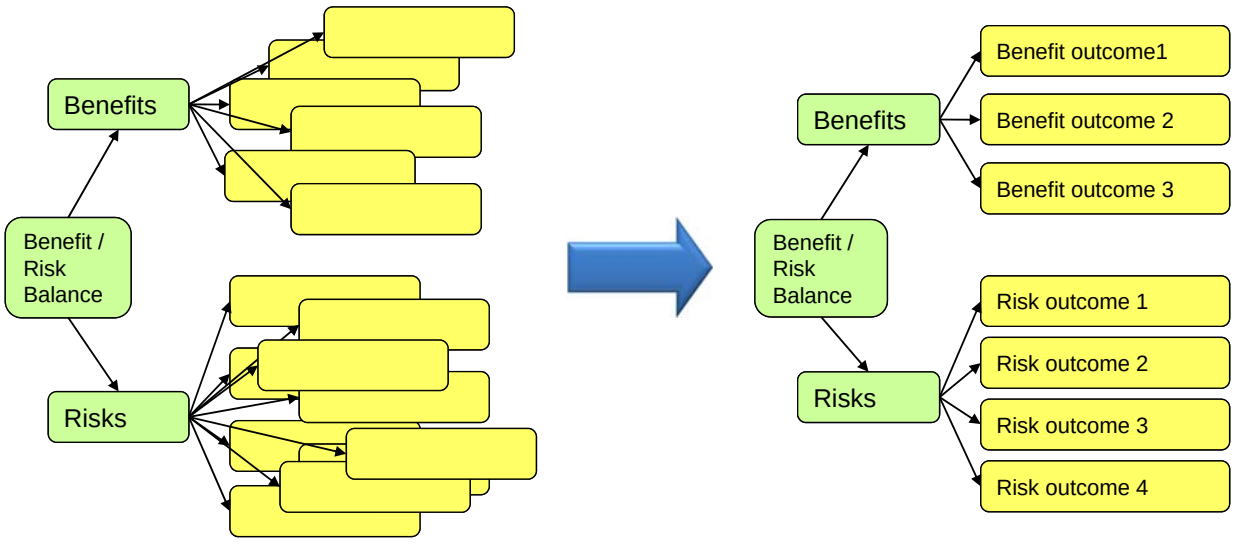
Framework Process – Value Tree

Establish a preliminary scope for the benefit-risk assessment by identifying and paring down potential benefit/risk outcomes



Framework can serve as basis for discussion with health authorities to prospectively frame the benefit-risk assessment

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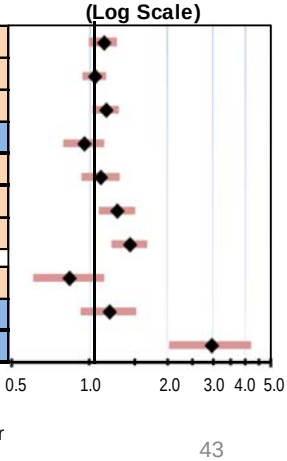
Key Benefit-Risk Summary Table
Triptans in Migraine

- Top-level representation of information in the framework
- The most critical view that decision makers will have on the data
- Use of graphic or tabular displays as needed to support rapid interpretation of information on multiple outcomes

		Outcome	Study Drug Risk (/1,000 pts)	Comparator Risk (/1,000 pts)	Odds Ratio (95% CI)
Benefits	↓ Pain	Rapid onset	271	248	1.13 (1.00,1.27)
		Headache relief	643	633	1.04 (0.94,1.15)
		Pain free response	383	349	1.16 (1.03,1.30)
		Sustained response	285	295	0.95 (0.80,1.14)
	↓ Sensitivity	Reduced sensitivity to sound and light	530	505	1.10 (0.94,1.30)
	↓ Other	Reduction in functional disability	540	480	1.28 (1.09,1.49)
		Reduction in nausea or vomiting	604	517	1.43 (1.22,1.67)
Risks	↑ Individual Risks	Transient triptans sensations	43	52	0.83 (0.61,1.14)
		CNS AEs	53	45	1.18 (0.92,1.51)
		"Chest-related" AEs	58	21	2.93 (2.04,4.20)



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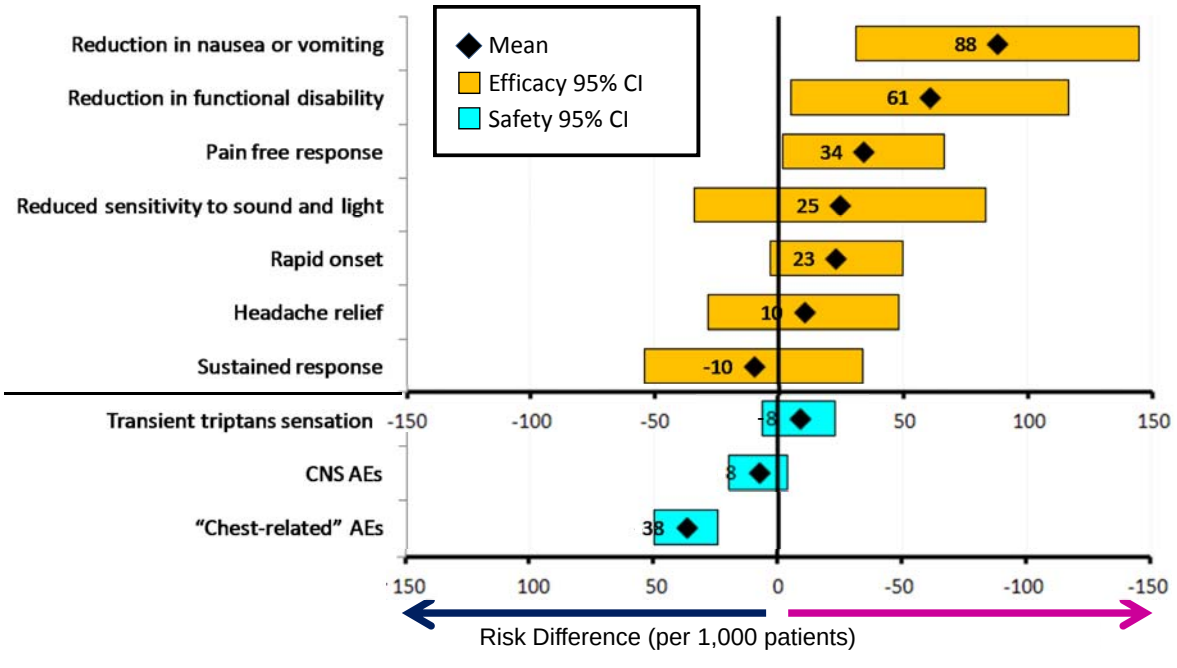
Risk Difference Forest Plot

Increasingly common for dichotomous endpoints in benefit-risk

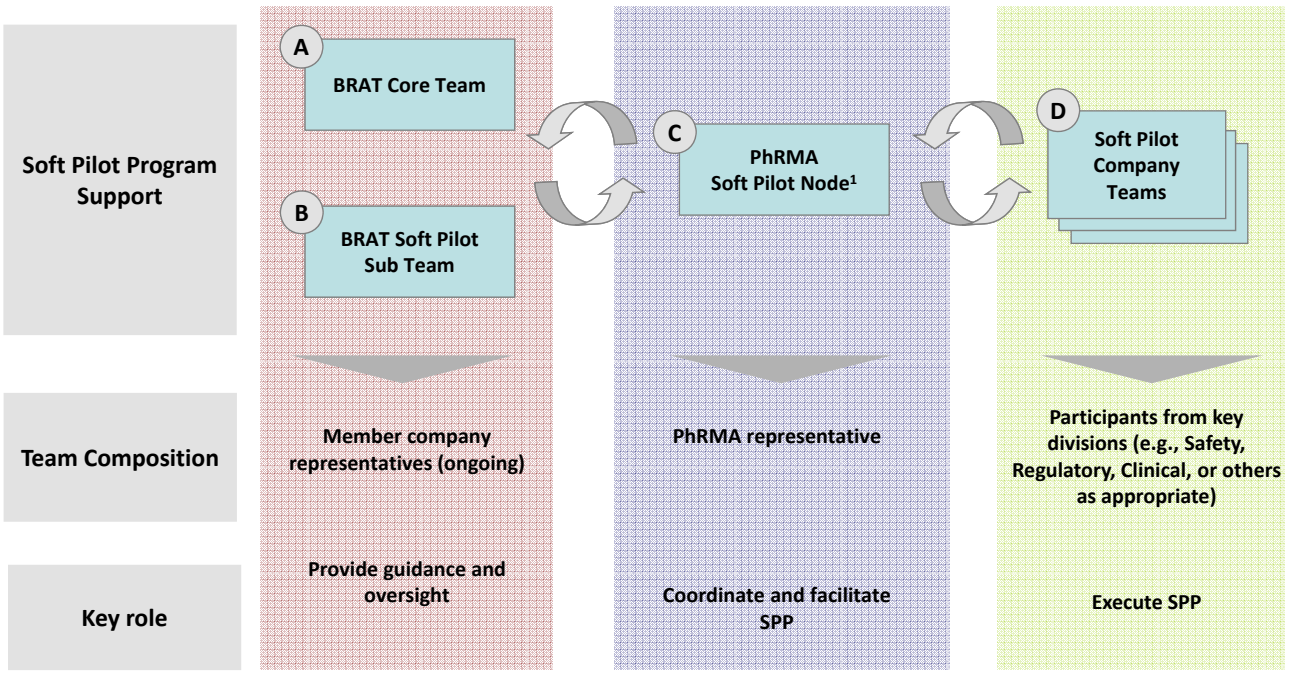


BRAT in the Real World

Soft Pilots

- 'bench work' on framework maxed out
- need real world demonstration of acceptable operating characteristics
- unbeatable test-bed for context-specific (read BR bucket) fine tuning

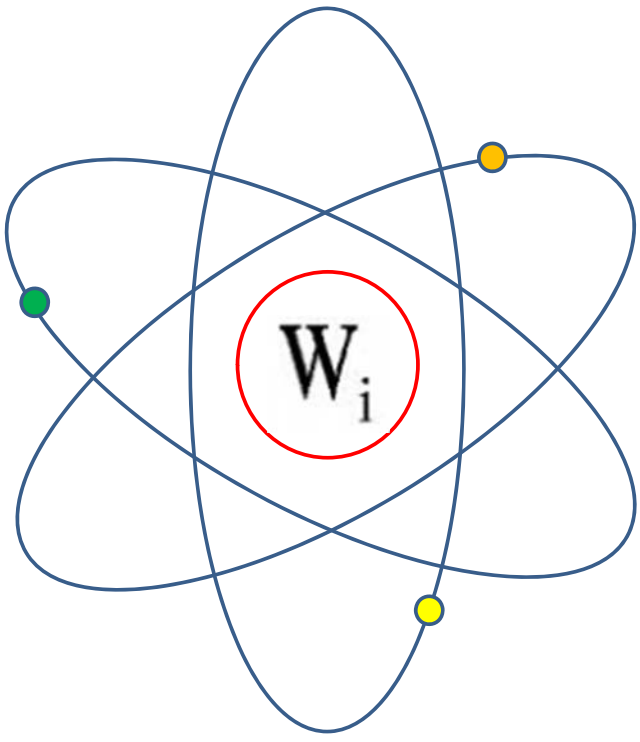
Four teams oversee execution of Benefit-Risk Soft Pilot Program (SPP)



BRAT Framework Transition

BRAT team handing framework to third party for further development.

Central role of values/weights!



Values & Weights

- regulatory agencies insist
- structured BR can't work without it
- BRAT Weighting Working Group:
  - draft white paper
  - therapeutic areas focus :
    - cardiovascular disease
    - pain management
    - psychiatry
- more from presenters later today ...

Fully Quantitative Models

Key Point

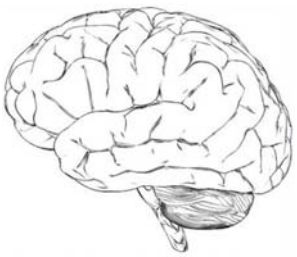
Frameworks and models are merely decisions aids and sound clinical judgment will remain the cornerstone of structured BR for the foreseeable future

"people decide, not models!" *

* L. Phillips. Improving the process of balancing benefits and risks in approving drugs. April 21, 2010

Like the BRAT framework, quantitative modeling, properly implemented, requires that stakeholders frame the issues and reach a common understanding about them.

Enquiring minds want to know



operating characteristics

Key Point

Regulators will not use models that reviewers do not understand!

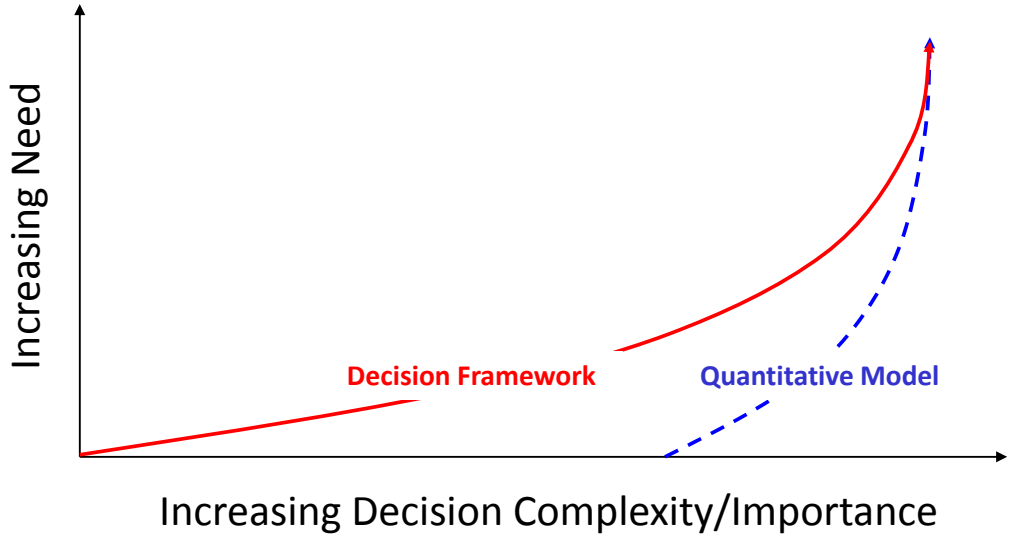
Key Point

Qualitative ~~vs.~~ Quantitative?

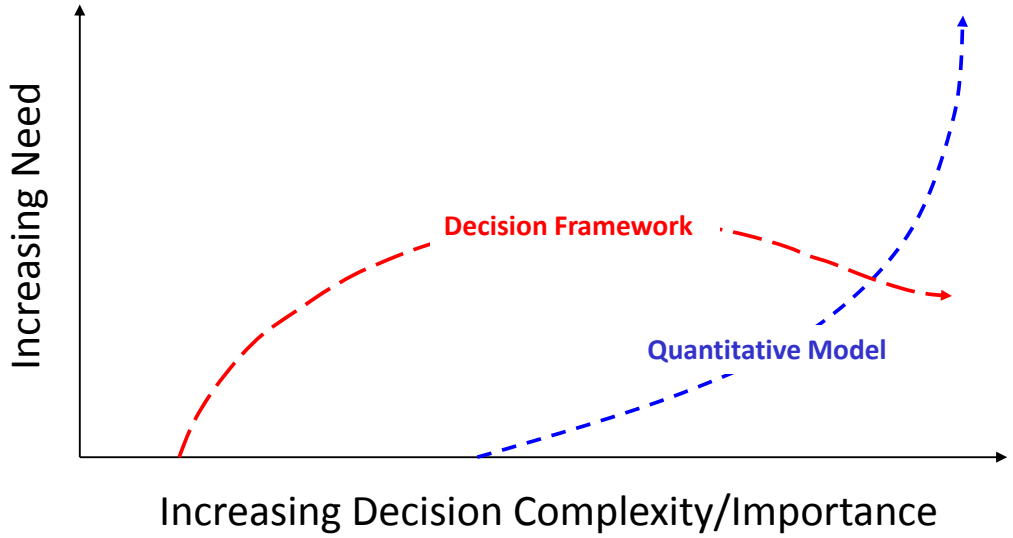
Qualitative, semi-quantitative & fully quantitative are c*omplimentary BR* decision aids!

Need for Structure in Decision-Making

Framework vs. Quantitative Model



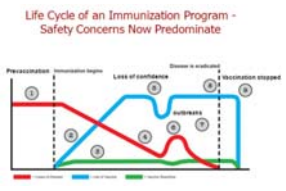
An Alternative? *



* adapted from Han Georg Eichler June 2011

Need for Fully Quantitative Models

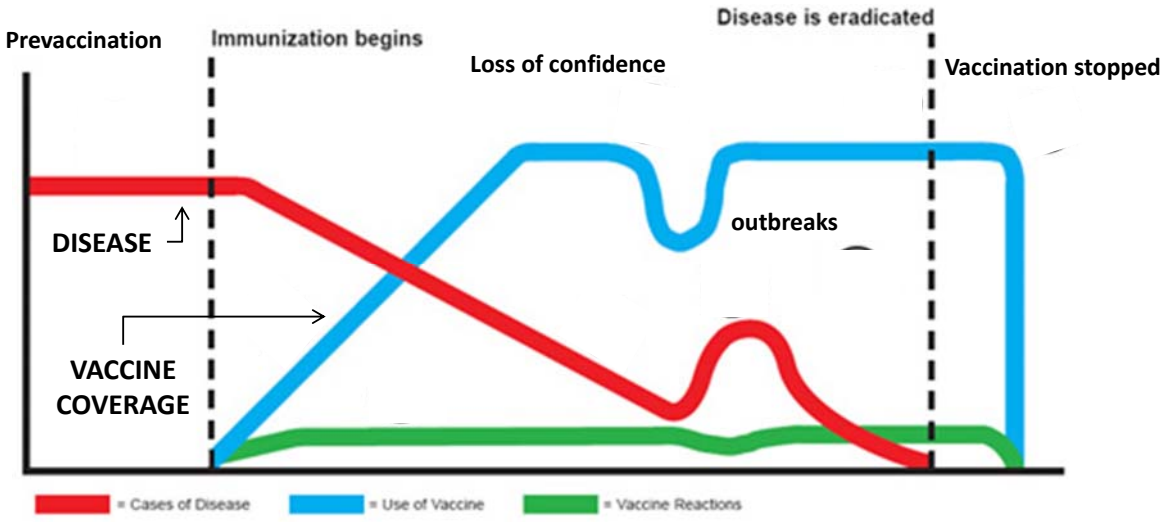
Time-dependent covariates &
Dynamic Modeling



"Beyond complexity lies simplicity"
Albert Einstein

Life Cycle of an Immunization Program

Safety Concerns Now Predominate



adapted from:
Chen RT et al. The Vaccine Adverse Event Reporting System (VAERS). Vaccine 1994;12:542-50

Dynamic Modeling

Time-dependent Outcomes

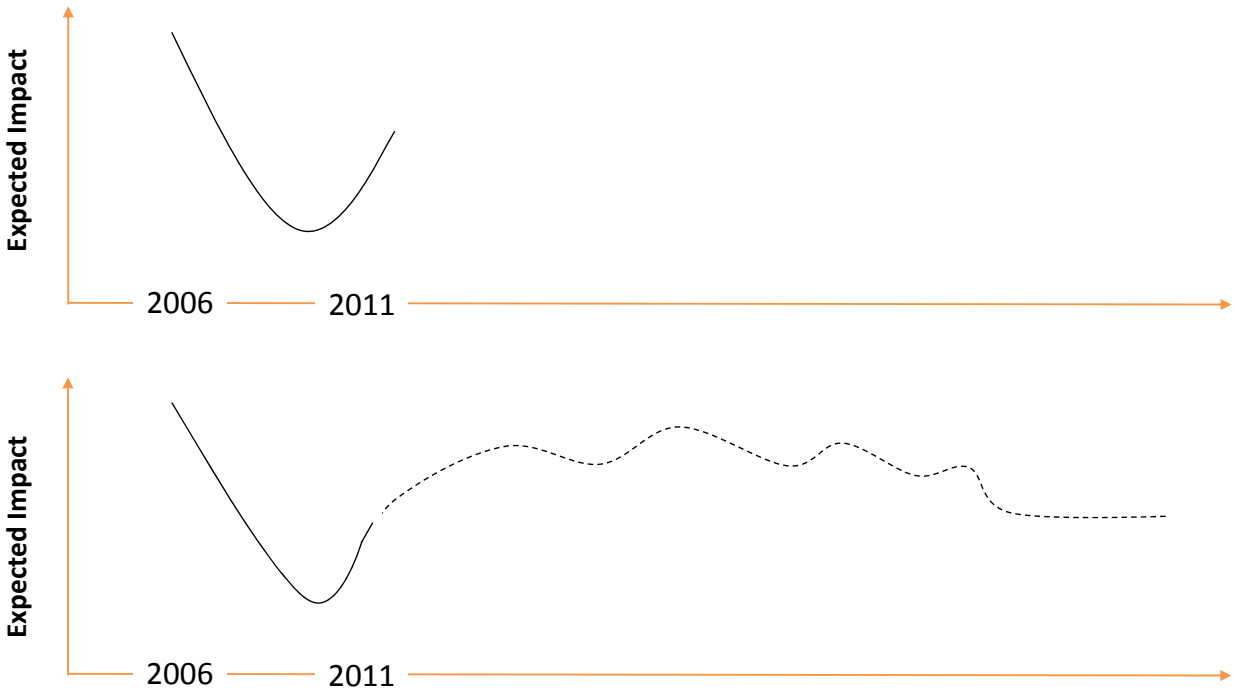
- qualitative approaches do not suffice
- examples of complexity that can be informed by fully quantitative modeling
  - Kalman Filters for prediction of time-dependent events in coronary care units
  - modeling benefit-risk balance conditioned on herd immunity, genetic drift and genetic shifts in influenza pandemics
- nascent dynamic modeling initiative involving regulators, academia and industry

“Prediction is very difficult ... especially about the future.” *

* Niels Bohr

Triangulating the Future

Quantitative Benefit-Risk



“… as simple as possible and no simpler” *

* Albert Einstein